

# CLINICAL TRIALS Broadcast

In Focus: RTOG Current Clinical Trials in Lung Cancer

## Overview

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The Radiation Therapy Oncology Group (RTOG) currently has 3 areas of focus in lung cancer: incorporating new technology into radiation therapy (RT); incorporating molecularly targeted agents into chemoradiation; and the role of prophylactic cranial irradiation (PCI) in preventing brain metastases.

In the first category, trial 0236 (phase II) is evaluating high-dose RT for early-stage lung cancer patients. Rather than administering standard radiation over 6 weeks, patients in this study are receiving very high-dose radiation over 3 or 4 weeks using the latest technology. Trial 0235 (phase II) is evaluating the role of positron emission tomography (PET) during treatment with chemoradiation. PET scan data are being collected before and after chemoradiation in order to determine whether this imaging has any role in predicting response and guiding treatment. Trial 0117 (phase I/II) is evaluating the use of high-dose radiation using conventional fractionation with a limited field for patients who are undergoing chemoradiation therapy. The phase III study in this category, 0412, was activated recently. All cooperative groups in North America are participating in this high-priority study exploring whether or not there is a survival difference between locally advanced non-small cell lung cancer (LA-NSCLC) patients who undergo radiation alone versus chemoradiation prior to surgery. Tissue will be collected from enrolled patients and analyzed using proteomic and genomic technology in order to assess the prognostic value of molecular markers. Patients will also undergo PET scans prior to and after radiation or chemoradiation to study its potential benefit in lung cancer.

The recently completed phase II study 0324 evaluated the benefit of chemoradiation plus cetuximab versus chemoradiation alone. A phase III study to evaluate the incorporation of this agent into chemoradiation therapy is awaiting approval by the National Cancer Institute.

Patients with small-cell lung cancer (SCLC) routinely receive PCI and it has been proven that this approach prevents metastasis and improves survival.<sup>1</sup> The phase II study 0212 is evaluating standard-dose PCI versus very high-dose PCI in order to determine whether a higher dose might be of more benefit. This trial was originally a European trial, and it has since been adopted in the United States. Finally, 0214 is a phase III trial of PCI in NSCLC. From studies over the past several years, it is apparent that the brain is the primary site of metastases in NSCLC patients who fail therapy.<sup>2</sup> Trial 0214 is evaluating the potential benefit of PCI in preventing brain metastases and improving survival compared to no PCI, which is the most common approach at this time. The planned enrollment of this study is approximately 1,000 patients and is open throughout North America.

## References

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2. Gaspar LE, Chansky K, Albain KS, et al. Time from treatment to subsequent diagnosis of brain metastases in stage III non-small-cell lung cancer: a retrospective review by the Southwest Oncology Group. *J Clin Oncol.* 23:2955-2961.

## Ongoing RTOG Trials in Lung Cancer

0117: 3D Conformal RT With Paclitaxel and Carboplatin for Inoperable Stage IIIA or IIIB NSCLC (Phase I/II)  
Targeted accrual: 73 (46 for phase II)  
Contact: (800) 600-3606

0212: PCI for Limited-Stage SCLC (Phase II/III)  
Targeted accrual: 264  
Contact: (305) 243-4210; awolfson@med.miami.edu

0235: Diagnostic Study of Fludeoxyglucose F18 PET for Pre-/Post-Treatment Assessment in Locally Advanced NSCLC (Phase II)  
Targeted accrual: 250  
Contact: (800) 533-3669

0236: Stereotactic Body RT for Inoperable Stage I/II NSCLC (Phase II)  
Targeted accrual: 52  
Contact: (214) 645-7637

0239: Cisplatin/Etoposide Plus Accelerated High-Dose RT for Limited-Stage SCLC (Phase II)  
Targeted Accrual: 71  
Contact: (800) 392-1611

0241: Irinotecan and Cisplatin Plus RT for Limited-Stage SCLC (Phase I)  
Targeted accrual: 12–36  
Contact: (888) 369-2571

0412: Neoadjuvant Cisplatin and Docetaxel With or Without Conformal RT Followed By Surgical Resection and Docetaxel in Newly Diagnosed Favorable-Prognosis Stage IIIA NSCLC (Phase III)  
Targeted accrual: 574  
Contact: 800-533-3669

## RTOG 0214

### A Phase III Comparison of Prophylactic Cranial Irradiation Versus Observation in Patients With Locally Advanced Non–Small Cell Lung Cancer

#### Background

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Among patients with LA-NSCLC approximately 50% develop central nervous system (CNS) metastases, the prevention of which is associated with improved quality of life (QOL) and survival. Studies have found that while treatment with radiation or radiation plus chemotherapy extends survival,<sup>1,2</sup> these therapies do not reduce brain relapse rates,<sup>3</sup> emphasizing the need for treatment directed specifically at CNS micrometastases.

Several studies have demonstrated the efficacy of combined chemotherapy, RT, and surgery in extending survival, and have also reported the brain to be among the most frequent sites of initial failure.<sup>4,7</sup> The significance of CNS failures associated with patients with prolonged survival has prompted inclusion of PCI into clinical trials.<sup>6,8,9</sup>

The majority PCI toxicity data are derived from studies with SCLC. Tolerance to PCI among NSCLC patients can only be inferred from prospective studies with serial longitudinal neuropsychologic testing of such patients treated with and without PCI. Thus far, late cognitive defects have not been detected among NSCLC patients who have undergone PCI.<sup>8</sup> In SCLC studies, PCI has been found to favorably impact QOL, decrease the incidence

of CNS metastases, and improve survival.<sup>10-12</sup> Despite these data, debate continues as to whether PCI should be part of the routine treatment of SCLC. PCI has been an optional part of multimodality therapy for NSCLC in clinical trials due to its effectiveness in decreasing CNS failures.<sup>6,8,9</sup> A survival benefit has not been proven in NSCLC. It is essential that a prospective randomized study evaluating survival and QOL benefit for PCI in NSCLC be conducted now, before strong biases prevent accrual to such a study.

RTOG 0214 is a randomized phase III trial that will compare PCI versus observation in patients with LA-NSCLC following the completion of definitive locoregional therapy, with patients having achieved a complete response (CR), partial response (PR), or stable disease (SD). Preliminary data from several studies support this study. Three randomized studies of PCI in LA-NSCLC have reported a decrease or delay in brain metastases associated with PCI.<sup>13-15</sup> In addition, several nonrandomized multimodality studies have demonstrated a potential benefit with PCI in the treatment of LA-NSCLC.<sup>6,8,9,16,17</sup>

Studies in which PCI influenced patterns of CNS failure administered radiation at total doses of 30–36 Gy and fraction sizes of 2–3 Gy.<sup>6,8,9,14</sup> A smaller fraction size (2 Gy) and a total dose of 30 Gy will be used in RTOG 0214 in order to minimize late tissue toxicity. This regimen has been found to decrease CNS metastases from 54% to 13% with no difference in neuropsychologic testing among patients who received PCI and those who did not at 4-year follow-up.<sup>8</sup>

The present study will include neuropsychologic testing using the Mini-Mental State Examination, the Hopkins Verbal Learning Test, and the Activities of Daily Living Scale. Data will be collected at study entry and repeatedly throughout the study. The European Organization for the Research and Treatment of Cancer QOL Questionnaire Core-30 and a 20-item Brain Cancer Module version of this questionnaire will both be used to assess QOL among patients enrolled in the study.

RTOG 0214 is a large-scale study aimed at evaluating whether or not PCI improves survival by safely decreasing the incidence of CNS metastases among LA-NSCLC patients who have received effective treatment. The successful prevention of CNS metastases will improve QOL and, among patients controlled extracranially, will improve survival.

#### References

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## Objectives

**Primary:** Determine whether PCI improves survival after effective logoregional/systemic therapy for patients with LA-NSCLC.

**Secondary:**

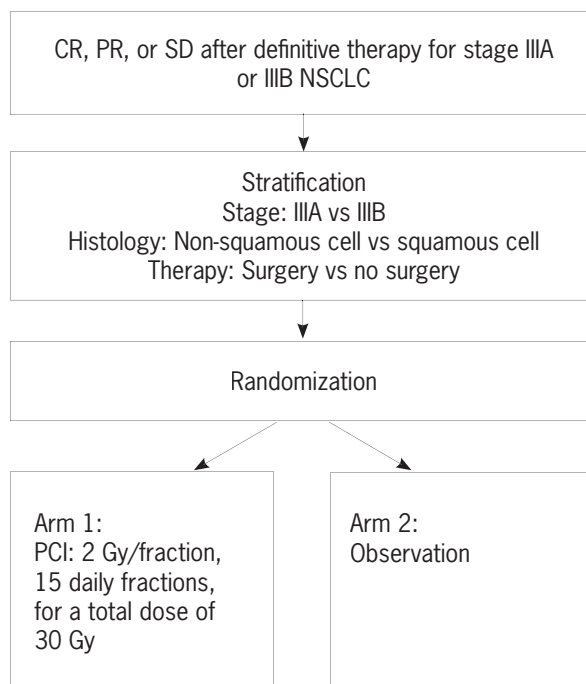
- Determine the neuropsychologic impact of PCI
- Determine the impact of PCI on QOL

- Determine the impact of PCI on the incidence of CNS metastases

## Key Eligibility Criteria

- Newly diagnosed stage IIIA or IIIB NSCLC having completed definitive locoregional therapy with CR, PR, or SD following therapy
- $\geq 18$  years of age
- Any acute/subacute grade  $\geq 3$  toxicities from previous therapy resolved to grade  $\leq 2$  at study entry
- No evidence of progressive disease or extracranial distant metastatic disease at study entry and no suspicion of CNS metastases within 6 weeks of study entry
- No prior cranial irradiation
- No participation in other phase III studies that have progression-free, disease-free, or overall survival as an endpoint

## Schema



## Targeted Accrual

1,058 patients (529 per arm) within 36 months

## Contact Information

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